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TOXICOLOGIC STUDIES WITH DIDYMIUM NITRATE AS MODIFIED BY SITE OF INJECTION AND WHOLE-BODY RADIATION

The rare-earth mixture didymium (as the nitrate) was administered to rats intraperitoneally, subcutaneously, and in wound implantation. Mortality and clinical sequelae were observed. When groups of these animals were subjected to 800 r of Co^{60} gamma irradiation, mortality was increased in all treatment groups. This increase was statistically significant in the intraperitoneal experiment and the combined effect appears to be synergistic.

The implications of an explosive reactor accident which may subject individuals to the combined injury of ionizing and thermal radiations, plus fission products from the element cores, led to studies of yttrium and lanthanum nitrate as toxic agents in rats (1). Several routes of administration were used and Co^{60} irradiation was given to certain groups in addition to the chemical compounds. Since it would be hard to imagine a single element being produced in a reactor accident or nuclear detonation, this study presents the results of treating animals with didymium nitrate. Didymium is a well-known mixture of the rare-earth group elements and contains both yttrium and lanthanum in addition to other elements. The experimental parameters are identical with those used in the first experiments with single elements except for the additional testing of implanted sand on surgically wounded animals and the observations of wound healing without the added complication of irradiation.

MATERIALS AND METHODS

Female Sprague-Dawley rats used in this experiment were obtained in a large shipment from a commercial supplier. The colony was maintained in air-conditioned quarters on Wayne Lab Blox "R" pellets and water ad libitum throughout the experiment. Cages 20 x 20 x 8 inches were used to house the rats in groups numbering less than 20.

Didymium nitrate solutions, when appropriate, were made up with sterile distilled water just before injection. Intraperitoneal injections were made on the ventral surface of the rat 2 inches below the rib cage. Subcutaneous injections and incisions for wounds were made on the back just above or slightly back of the pectoral girdle. Prior to all injections or incisions, the rats were anesthetized by intraperitoneal injections of pentobarbital sodium at a dose of 4 mg./100 gm. of body weight. An area on the back of the animal was shaved and swabbed with a tincture of merthiolate®; a 1-inch incision was made with a scalpel and the material (in powder form) was placed within the wound. The incision was closed with wound clips and then the area covered with Spraygel.

Irradiated animals received Co^{60} gamma rays at a dose rate of 800 r/minute. The exposure facility (2) and chemical dosimetry (3) used have been described elsewhere.

Didymium nitrate$\cdot 6H_2O$ was obtained from the Lindsay Chemical Co. A typical analysis is shown in table I.

Intraperitoneal injections of didymium nitrate in the presence and absence of whole-body radiation

The rare-earth and radiation program was carried out as outlined in table II. Appropriate rats were exposed to 800 r of Co^{60} gamma rays.

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This work was accomplished at the Radiobiological Laboratory of the University of Texas and the United States Air Force, Austin, Tex.

Four hours later, rats in all groups were anesthetized with pentobarbital sodium and injected with didymium nitrate$\cdot 6H_2O$ in water at a dose of 400 mg./kg. body weight. In the group of 21 rats receiving didymium alone, only 3 animals died – on days 3, 5, and 9 (fig. 1). In the group of 22 rats receiving didymium plus 800 r, 20 animals died. These deaths occurred during two major periods. Twelve animals died from days 2 to 6, the maximum number of deaths occurring on day 4; and 7 animals died from days 10 to 13, the maximum number of deaths occurring on day 10 (fig. 1). In a group of 8 animals receiving only 800 r of Co^{60} irradiation, no mortalities were seen in 30 days (fig. 1). A chi-square statistical treatment of the combined numbers was accomplished and the difference in mortality was significant ($P < .01$).

TABLE I

*Approximate composition of the contained rare-earth oxide in didymium materials**

Rare-earth oxides	Percent
La_2O_3	45 - 46
CeO_2	1 - 2
Pr_6O_{11}	9 - 10
Nd_2O_3	32 - 33
Sm_2O_3	5 - 6
Gd_2O_3	3 - 4
Y_2O_3	0.4
Other rare-earth oxides	1 - 2

*Bulletin D-1, Lindsay Chemical Co., West Chicago, Ill.

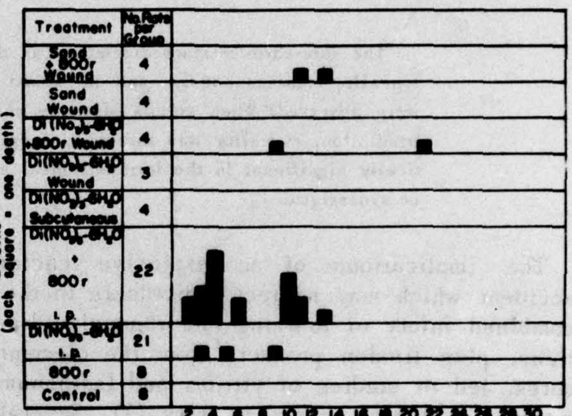

FIGURE 1

Thirty-day lethality in irradiated and normal rats treated with didymium nitrate.

TABLE II

Protocol

*Subcutaneous injection study**

	$Di(NO_3)_3\cdot 6H_2O$ 160 mg.	$NaNO_3$ 160 mg.	0.9% NaCl
Number of rats per group	4	4	4

*Total volume for each injection was 0.8 ml.

Wound study†

	Sand 400 mg./kg B. W.	Sand + 800 r 400 mg./kg. B. W.	$Di(NO_3)_3\cdot 6H_2O$ 400 mg./kg. B. W.	$Di(NO_3)_3\cdot 6H_2O$ + 800 r 400 mg./kg. B. W.
Number of rats per group	4	4	4	4

†All materials in wound study were administered in powder form.

Subcutaneous injection of aqueous solutions of didymium nitrate, sodium nitrate, and saline

Prior to injection, all rats were anesthetized with pentobarbital sodium. The subcutaneous injection program was carried out in accordance with table II. Up to 30 days, neither sodium nitrate or saline-injected rats exhibited any signs of epilation or abscess formation and their general appearance was normal. Among the animals receiving the didymium, epilation and necrosis in the area of injection were evident in 3 animals by day 8. A fourth rat demonstrated a large nodule laterally behind the right front leg; this nodule was necrotic and epilated. By day 10, all animals possessed nodules and these areas of abscess were draining. The x-ray plate, shown in figure 2, demonstrates clearly the abscesses present in these rats by day 10 postinjection. Further examples of the appearance of the rats receiving subcutaneous material may be seen in figures 3 and 4. The condition of these animals remained the same, so far as could be visually observed, from day 10 to day 30.

Effect of didymium nitrate, sodium nitrate, and sand on wound healing

All of the rats in this group were anesthetized with pentobarbital sodium. Once the incision was made, the powdered material was placed in the wound, the incision closed with wound clips, and the area covered with Spraygel. Fifteen days posttreatment, wound animals which had been impregnated with sodium nitrate and wound animals which had received 800 r were healed. Eight animals received sand (washed with distilled water and dried) and 4 of these rats were given 800 r Co^{60} gamma rays. Two of the 4 irradiated animals were dead by day 13 (fig. 1), whereas all of the rats which were not irradiated survived 30 days. These wounds were healing well by day 6 posttreatment and progress appeared entirely normal. By day 30, no evidence of incision or implant could be seen (fig. 4). The irradiated animals progressed in the same manner except at a somewhat slower rate and with a slight loss in weight during week 2 postirradiation.

Seven animals received didymium nitrate$\cdot 6H_2O$ in wounds. Four of these rats were irradiated with 800 r of Co^{60} gamma rays. Through day 7 postirradiation, healing proceeded in an apparently normal manner and could not be distinguished visually from the sand or sodium nitrate animals. On the 8th day, 2 rats in each group had small nodules near the wounds; the irradiated animals appeared sick. On day 9, all wounds in these two series were draining and

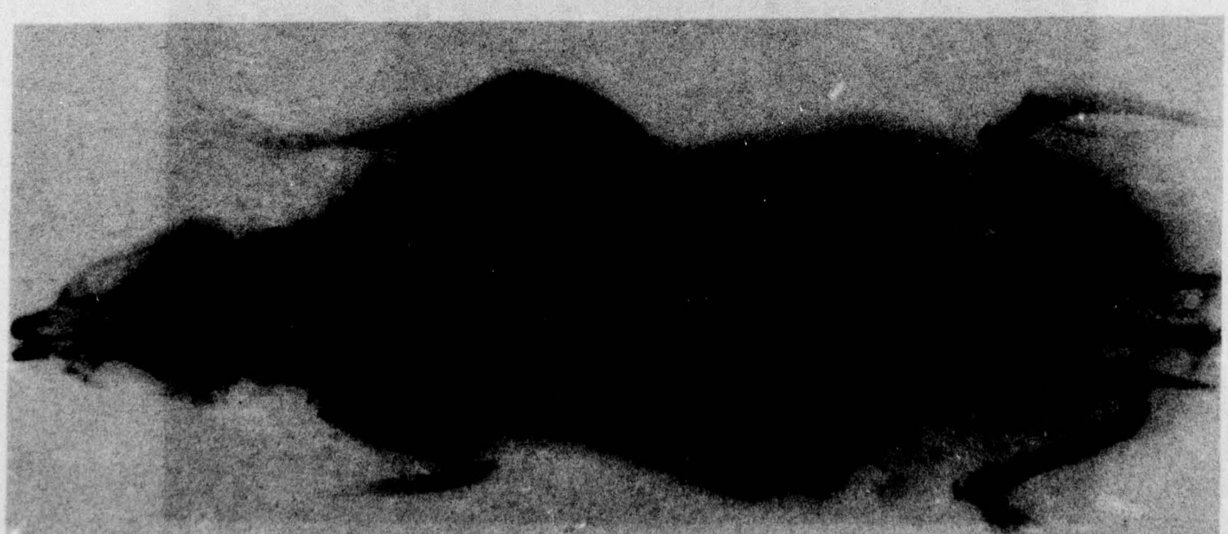

FIGURE 2

X-ray of abscess following subcutaneous injection of 160 mg. of didymium nitrate.

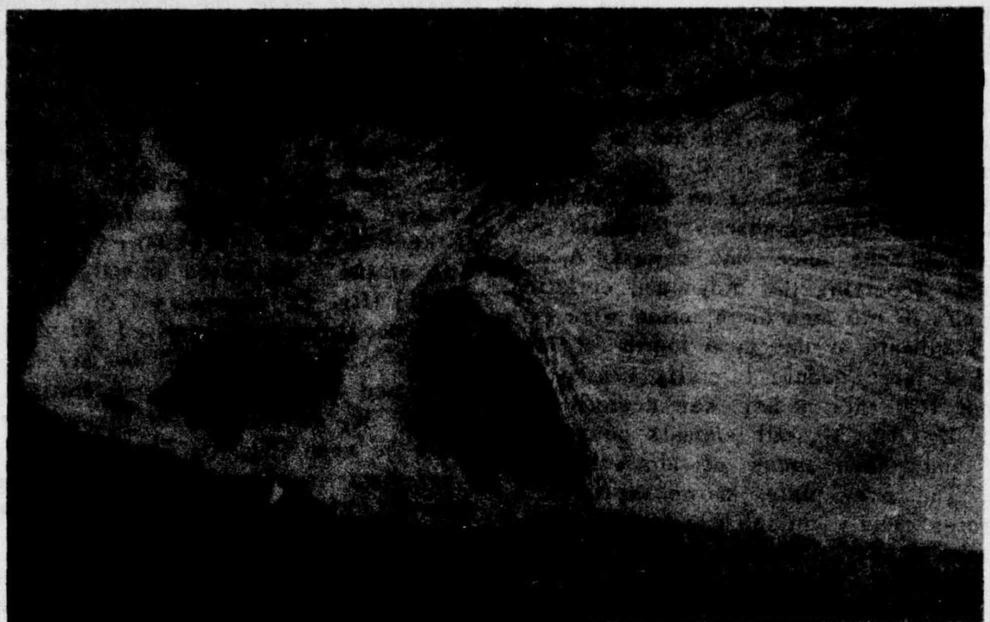

FIGURE 3

Photograph of wound occurring at the site of a subcutaneous injection of didymium nitrate.

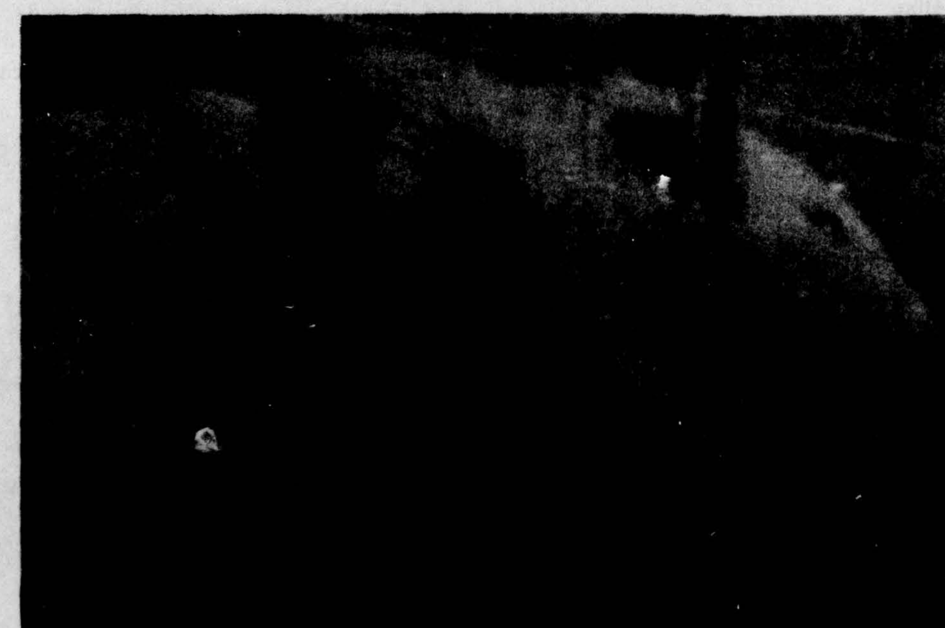

FIGURE 4

Photograph showing the abscess and wound occurring at the site of a subcutaneous injection of didymium nitrate.

FIGURE 5

Photograph showing the appearance of typical wound animals 30 days after implantation of sand or didymium nitrate.

starting to reopen and the first of 2 animals receiving didymium plus 800 r died. On days 10 and 11 postincision, draining, inflammation, and irritation were noted in all 6 survivors. The second irradiated rat died on day 21. Figure 5 shows the condition of 4 typical wound animals on day 30 after the treatment.

DISCUSSION

It is interesting to note that while only the larger groups of animals gave statistically significant results, all the groups which received radiation plus didymium showed greater mortality than those receiving chemical material alone. In the intraperitoneal injection groups, additivity – indeed, synergism – of radiation and the didymium is evident and is similar to the results indicated in experiments with yttrium and lanthanum alone (1). Further comparison between these two studies has not been made since animals of different sexes were used.

In the experiments with didymium, the contribution of yttrium to the observed mortality must be essentially ruled out since there is so very little present (table I). Neodymium and praseodymium are major constituents of didymium; like other rare earths, they are reported to be poorly absorbed from the gastrointestinal tract (4). Maxwell and Bischoff (5) have reported that in the rat the LD_{50} intravenous dose of $Pr(NO_3)_3$ is approximately 12 mg./kg. body weight. Subcutaneous injection of praseodymium chloride in the mouse requires 2,500 mg./kg. body weight to reach an LD_{50} mortality (6). Some 4 hours after subcutaneous injection of cerium and praseodymium, less than 1 percent of the dose had been absorbed and most of this portion was in the bone (4). Neodymium appears to be about 1½ times less toxic than praseodymium when administered subcutaneously. No extremely reliable information is available on the $LD_{50/30}$ dose in rats for the intraperitoneal injection of elements such as neodymium, praseodymium, gadolinium, and samarium. Kyker and Cress have very recently reported on the intravenous toxicity of these elements (7). Kyker also reports that the elements yttrium and lanthanum are much more toxic intraperitoneally than had been previously supposed.

Certainly, it would appear that, so far as comparisons can be attempted with studies such as those accomplished in male rats with yttrium and lanthanum (1), the qualitative and quantitative effects of didymium are the same as these elements when radiation is not involved. In the presence of radiation, didymium is probably much more dangerous. It is impossible at the present time to state what the contribution of the additional elements in the mixture may be or the distribution of this contribution.

In our previous studies, all animals which were subjected to the implantation of material in wounds were also irradiated. In this experiment, sand and didymium were implanted in groups of animals which were not irradiated. Some deaths resulted within 30 days among the irradiated animals but not among the nonirradiated animals. Whether or not the irradiation definitely complicates the clinical picture of the wound healing is extremely difficult to assess; it would appear that there is a somewhat delayed response in the irradiated rats.

It is very probable that the use of less soluble salts of the rare-earth elements such as the oxides, would alter these results considerably and indeed be more specific to a reactor accident. A study now under way will compare the effects of the oxide and the nitrate of a rare-earth mixture.

SUMMARY

The rare-earth mixture didymium (as the nitrate) was administered to rats intraperitoneally, subcutaneously, and in wound implantation. Mortality and clinical sequelae were observed. When groups of these animals were subjected to 800 r of Co^{60} gamma irradiation, mortality was increased in all treatment groups. This increase was statistically significant in the intraperitoneal experiment and the combined effect appears to be synergistic.

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